Radical Addition to Strained σ-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters

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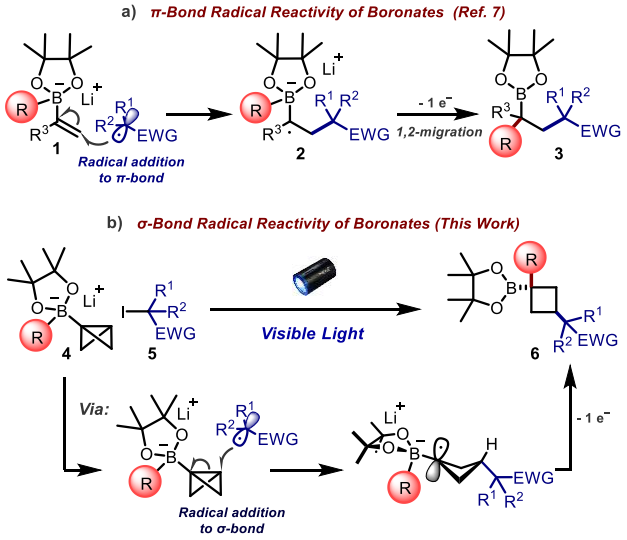
Supporting Information Placeholder

ABSTRACT: Whilst radical additions to π-bonds are well established, additions to σ-bonds are far less explored. We have found that electron deficient radicals derived from alkyl iodides under visible light irradiation add to the central strained bond of bicyclobutyl (BCB)-boronate complexes and lead to 1,3-alkyl disubstituted cyclobutyl boronic esters in high yields, with full stereospecificity and high levels of stereoselectivity. Novel cyclobutyl-substituted structures, including peptide and steroid boronic ester derivatives can be accessed. Additionally, although the use of electron-rich alkyl iodides as radical precursors was found to be ineffective, an alternative route involving alkylsulfonylation of the BCB-boronate, followed by reductive desulfonylation provided access to simple alkyl substituted cyclobutane products.

The field of radical chemistry[1] has witnessed a renaissance over the last decade,[2] triggered largely by the introduction of photoredox methods (electron transfer photocatalysis)[3-4] for the generation of open-shell species under mild conditions. The radicals generated have been utilized in a broad array of reactions including addition to π-systems (e.g. olefins, alkynes, aromatics),[2-4] radical-metal recombination[5] and radical-radical cross-coupling.[6]

We and others recently showed that electrophilic radicals readily add to π-bonds of unsaturated boronate complexes **1** (Scheme 1a).[7] Subsequent one-electron oxidation of the resulting intermediate radical anion **2** triggered a 1,2-metallate rearrangement leading to densely functionalized boronic esters **3**. We questioned whether less activated σ-bonds, embedded in a strained molecule,[8] could undergo analogous radical reactivity as this would significantly enhance the scope of both boron and radical chemistry. In support of this hypothesis, the addition of radicals to exceptionally strained σ-bonds has been observed,[9] although studies in this area remain limited. Specifically, we sought to add radicals to the central σ-bond of a strained bicyclobutyl (BCB)-boronate complex **4** (Scheme 1b), which we recently showed was capable of reacting with electrophilic palladium(II) intermediates.[10] Following radical addition, one-electron oxidation[7] would trigger a 1,2-metallate rearrangement[11] leading to cyclobutyl boronic esters **6**. Not only does this proposal present novel reactivity between boronate complexes and radicals, but it also offers a mechanistically distinct method to prepare challenging polysubstituted cyclobutanes.[12] Such entities have the potential to open up considerable chemical space due to the three readily diversifiable positions (radical precursor,[4] boronic ester substituent, and the boron atom[13] itself). Furthermore, cyclobutanes are of increasing interest in medicinal chemistry,[14] adding significant motivation for developing this methodology. Herein, we show that radicals can indeed add to the central σ-bond of a strained BCB-boronate complexes, thereby providing a stereocontrolled synthesis of 1,3-dialkyl substituted cyclobutyl boronic esters **6**.

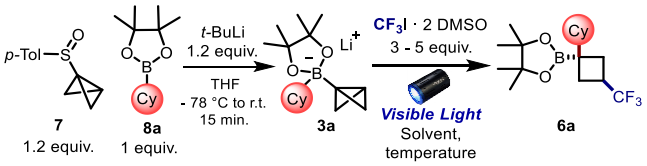
Scheme 1. a) Radical addition to π-bonds of unsaturated boronate complexes. b) Proposed radical addition to σ-bonds of BCB-boronate complexes.



We began our studies by focusing on developing a radical trifluoromethylation process,[2c] as the trifluoromethyl group is a highly sought-after moiety in medicinal chemistry.[15] For the optimization studies, the BCB-boronate complex **3a** was generated *in situ* by adding *t*-BuLi to a mixture of sulfoxide **7** and cyclohexyl boronic acid pinacol ester **8a** in THF. An excess (5 equiv.) of trifluoromethyl iodide-DMSO complex and 1 mol% of the photocatalyst $Ru(bpy)_3^{2+}$ were then added under blue LED irradiation. After 16 h we were delighted to find that the expected boronic ester **6a** was formed in good yield and moderate diastereoselectivity (Table 1, entry 1). A brief solvent screen showed that THF was superior to DMSO and MeCN (entries 2-3). Performing the reaction at -78 °C[16] was found to significantly improve the process, providing the desired compound **6a** in high yield and as a single diastereoisomer (entry 4; stereochemistry established by ^{1}H-NMR NOE analysis,

see SI for details). In line with our previous studies with vinyl boronates,[7b] we found that the photocatalyst was unnecessary for the process (entry 5). Finally, the loading of radical precursor could be decreased to 3 equivalents, and the reaction time shortened to 1 hour, without any loss in reaction efficiency (entry 6). A control experiment highlighted the importance of light, as only traces of **6a** were observed in the absence of blue LED irradiation (entry 7). Finally, performing the reaction in the presence of a radical inhibitor (TEMPO) led to complete inhibition (entry 8), and to the detection of the TEMPO–CF_3 adduct (see SI), which is indicative of the involvement of radical species in the process.

Table 1. Optimization Studies.

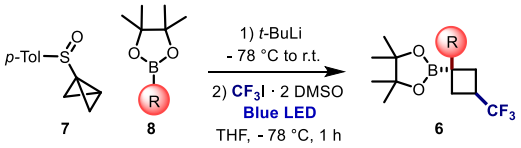


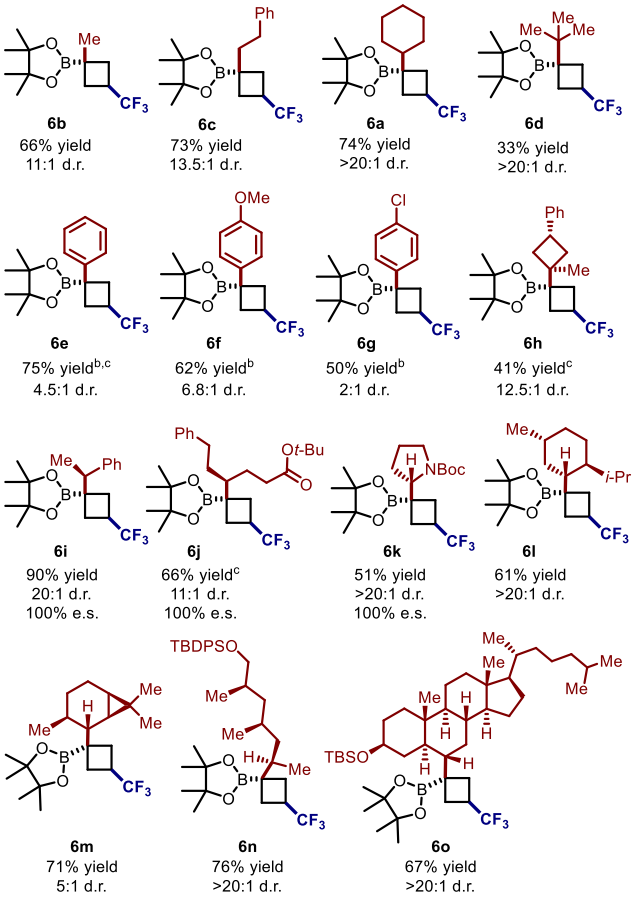
Entry[a]	Solvent	T (°C)	**6a** (%)[b]	d.r.[c]
1[d]	THF	25	66	5:1
2[e]	DMSO	25	52	6:1
3[e]	CH_3CN	25	46	5:1
4[d]	THF	-78	73	>20:1
5	THF	-78	75	>20:1
6[f]	THF	-78	79 (74)	>20:1
7[g]	THF	-78 to 25	6	5:1
8[h,f]	THF	-78	0	-

[a] All the reactions performed on a 0.1 mmol scale, light source: Kessil blue LED lamp (see SI), reaction time: 16 h. Cy: cyclohexyl. [b] ^{19}F-NMR yield using trifluorotoluene as internal standard, number in parentheses is the isolated yield of a 0.2 mmol scale reaction. [c] Determined by ^{19}F-NMR. [d] 1 mol% of $Ru(bpy)_3(PF_6)_2$ used. [e] 1 mol% of $Ru(bpy)_3Cl_2$ used. [f] Reaction carried out with 3 equiv. of $CF_3I{\cdot}2DMSO$, reaction time: 1 hour. [g] Reaction carried out without blue LED irradiation. [h] Reaction carried out in the presence of 1 equiv. of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

With the optimized conditions in hand, we explored the scope of the radical trifluoromethylation reaction by varying the structure of the starting boronic ester. The reactions were found to occur with high diastereoselectivity, and simple chromatographic separation of the isomers allowed isolation of the products as single diastereoisomers. A variety of alkyl groups could be accommodated on the boronic ester starting material, from a simple Me group up to a *t*-Bu group, showing that the reaction tolerates the full spectrum of steric demand and affords products **6b-d** with high stereoselectivity (Scheme 2). Aromatic boronic esters were also successfully employed, although only moderate levels of diastereoselectivity were achieved (**6e-g**).[17] A cyclobutyl boronic ester was also explored, giving the strained boronic ester **6h**, featuring two adjacent cyclobutyl rings with high diastereoselectivity. Enantioenriched boronic esters featuring a chiral center in the α-position gave **6i-k** with complete retention of stereochemistry. The pyrrolidine boronic ester substrate is especially noteworthy as this is normally a poor migrating group[18] but worked well under our standard conditions giving **6k** in good yield and with high stereocontrol. In addition, cyclobutyl boronic esters bearing complex chiral structures and biologically relevant substituents could be obtained through this methodology with high stereocontrol (**6l-o**).

Scheme 2. Scope of boronic esters for the radical trifluoromethylation reaction[a]

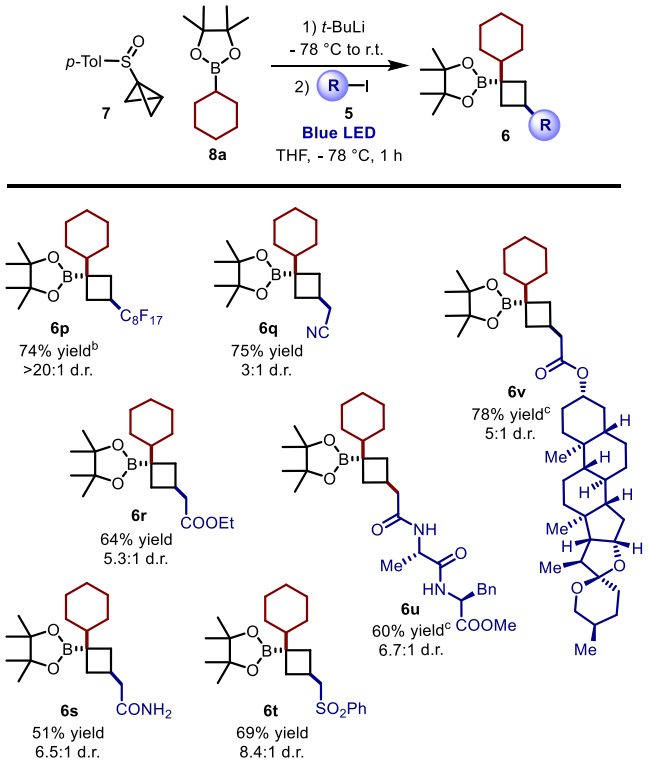




[a] Unless noted otherwise, isolated yields of single diastereoisomer in reactions carried out under a nitrogen atmosphere, with 1.2 equiv. of **7**, 1.0 equiv. **8** and 3 equiv. of $CF_3I{\cdot}2DMSO$, using Schlenk techniques on a 0.2 mmol scale. Diastereomeric ratio measured by ^{19}F-NMR analysis of the crude reaction mixture and refers to stereochemistry across the cyclobutane ring: the migration was in all cases observed to be stereospecific with respect to the migrating carbon. [b]Reaction time: 24 hours, propionitrile used as solvent. [c] Compound isolated as a mixture of diastereoisomers.

We then sought to explore the scope of radical precursors that could be employed. Longer perfluoroalkyl chains could be used, resulting in similarly high yield and stereoselectivity (Scheme 3, compound **6p**). A number of alkyl halides carrying electron withdrawing groups – including nitriles, esters, primary amides and sulfones – reacted with high yield and moderate to good diastereoselectivity (**6q-t**). The stereoselectivity of the process was observed to follow the trend CN < COOEt < SO_2Ph, indicating that steric factors influence the outcome of the reaction. Remarkably, dipeptide **6u** and tigogenin derivative **6v** could also be efficiently synthesized from radical precursors derived from the corresponding biologically relevant molecule, showcasing the applicability of this process for late stage functionalizations.

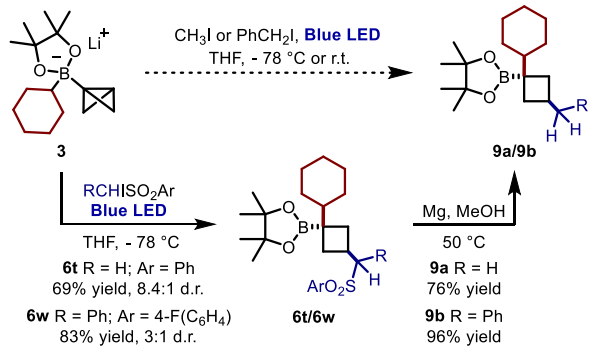
Scheme 3. Scope of radical precursors[a]



[a] Isolated yields of mixtures of diastereoisomers in reactions carried out under a nitrogen atmosphere, with 1.2 equiv. of **7**, 1.0 equiv. **8a** and 2 equiv. of iodide **5**, using Schlenk techniques on a 0.2 mmol scale. Diastereomeric ratio measured by ^{1}H-NMR analysis of the crude reaction mixture. [b] $Ru(bpy)_3(PF_6)_2$ (1 mol%) was used. [c] Reaction time: 24 hours.

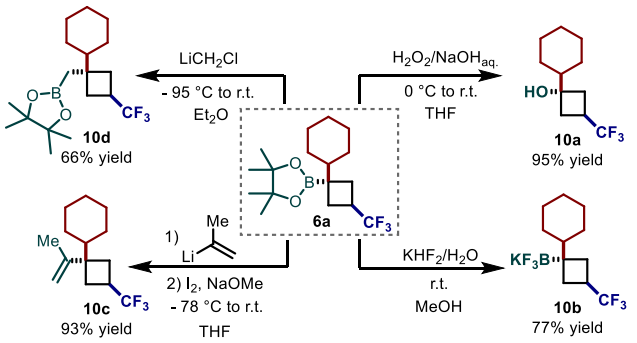
Unfortunately, non-activated alkyl iodides (e.g. benzyl iodide, methyl iodide) were found to be unreactive in the process, presumably because the polarity of the electron rich radical did not match with the polarity of the electron rich BCB-boronate, limiting the scope of the methodology. To overcome this limitation, we considered the use of sulfones as traceless activating groups.[19] Pleasingly, sequential radical alkylsulfonylation followed by reductive cleavage of the sulfone enabled access to alkylated products **9a** and **9b** in high yields (Scheme 4). Interestingly, the cyclobutylmethyl radical intermediate involved in the desulfonylation did not undergo ring opening [$k=4.5\cdot10^2$ s^{-1}],[20] showing that reduction/protonation are faster processes.

Scheme 4. Strategy to introduce simple alkyl groups



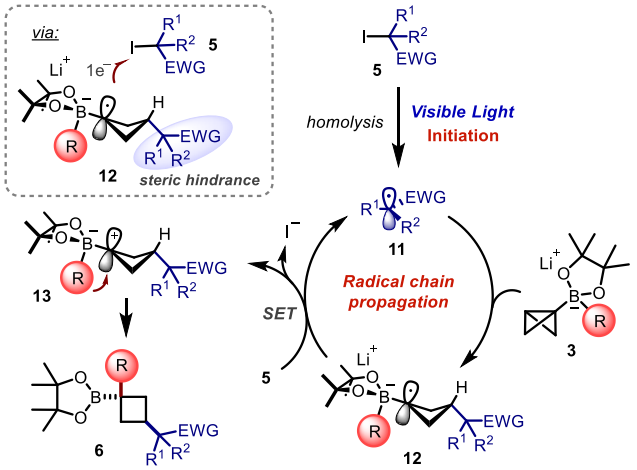
The synthetic utility of the products was demonstrated by carrying out a number of functional group interconversions of the boronic ester. For example, cyclobutane **6a** underwent stereospecific oxidation to alcohol **10a**, conversion to potassium trifluoroborate salt[21] **10b**, Zweifel olefination[22] to give alkene **10c**, and Matteson homologation[23] to afford boronic ester **10d** (Scheme 5).

Scheme 5. Product functionalization reactions



The mechanism of this photochemical radical reaction of BCB-boronate complexes likely bears similarities to that previously reported for vinyl boronate complexes.[7b] We propose that the light sensitive alkyl iodide undergoes photolytic initiation generating radical **11**, which adds to the strained central σ-bond of BCB-boronate **3** leading to the electron-rich radical anion **12** (Scheme 6). Single electron transfer to another molecule of alkyl iodide **5** regenerates radical **11** and forms zwitterionic species **13**, which undergoes fast 1,2-metallate rearrangement to give the final product **6**.[24] We believe that the single electron-transfer step is also the stereoselectivity determining step. As depicted in Scheme 6, alkyl iodide **5** approaches radical intermediate **12** from the less hindered face of the cyclobutane ring, away from the alkyl iodide-derived substituent. As the electron is transferred, 1,2-migration occurs on the opposite lobe of the p orbital before the molecule has time to undergo bond rotation around the C^+–B bond. This accounts for the *cis*-relationship between the two alkyl groups in **6.**

Scheme 6. Proposed reaction mechanism



In conclusion, we have shown that bicyclobutyl boronate complexes are excellent radical traps for electrophilic radicals, providing a novel visible light-mediated three-component coupling. Furthermore, the reaction can be conducted in the absence of photocatalysts. The reactions occur with moderate to excellent diastereoselectivity, are fully stereospecific, and allow the synthesis of complex chiral cyclobutanes, including peptide and steroid derivatives. The reactivity is induced by strain release-driven radical

addition to σ-bonds, a pathway that will no doubt find further application in the synthesis of cyclobutyl-containing natural products and drug candidates

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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(16) Illumination at low temperature could be effectively, practically and reproducibly achieved by using a commercially available high-power LED light source, a cryostat and a mirror-walled dewar. For experimental details and a picture of the reaction set-up, see Supporting Information.

(17) We believe that the lower stereoselectivity observed for aromatic boronic esters, when compared to alkyl boronic esters, results from these substrates reacting via a different mechanism, in which the radical anion intermediate can undergo 1,2-aryl migration prior to single electron oxidation. This is discussed in more detail in the Supporting Information.

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(24) Presently, we cannot exclude the possibility of an atom transfer mechanism. In this scenario, radical anion **12** abstracts an I atom from another molecule of **5**, generating radical **11** and an α-iodo boronate complex, which is expected to undergo 1,2-migration rapidly to afford product **6** (see ref. 7).

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